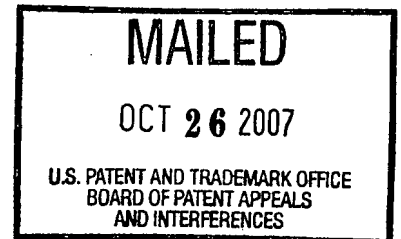


1 RECORD OF ORAL HEARING
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3 UNITED STATES PATENT AND TRADEMARK OFFICE
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6 BEFORE THE BOARD OF PATENT APPEALS
7 AND INTERFERENCES
8

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10 Ex parte SAUL TZIPORI,
11 RAMASWAMY BALAKRISHNAN, and
12 ARTHUR DONOHUE-ROLFE
13

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15 Appeal 2006-2945
16 Application 10/041,958
17 Technology Center 1600
18



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20 Oral Hearing Held: August 8, 2007
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24 Before DONALD E. ADAMS, LORA M. GREEN, and NANCY J. LINCK,
25 Administrative Patent Judges
26

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1 The above-entitled matter came on for hearing on Wednesday,
2 August 8, 2007, commencing at 9:05 a.m., at the U.S. Patent and Trademark
3 Office, 600 Dulany Street, Alexandria, Virginia, before Carol A. Lowe,
4 RPR.

5 JUDGE ADAMS: We're familiar with your issues. You have
6 20 minutes. And you can begin when you're ready.

7 MS. PABST: Okay. Again, we want to thank you all for the
8 opportunity to be here today.

9 This is a case involving a product that we think is really, really
10 important. And Dr. Tzipori is going to update you as far as where the
11 clinical trials in the development of this product is as well as hopefully give
12 a brief overview of the technology and some of the differences with the prior
13 art and walk a little bit through the example data to show you where those
14 important features are proven in the application and then hopefully answer
15 any questions that you might have.

16 Again, the technology here was the discovery that a very bad
17 disease, this HUS that resurfaced again last year with the spinach outbreaks,
18 is caused not just by an organism E. coli that was known to cause this
19 disease but the fact that the toxin -- that one of the several toxins in this
20 organism, the Shiga-like toxin II, is critically important not to the disease of
21 the diarrhea and infection but to the very, very bad side effects, the systemic
22 complications that lead to death and permanent disability and that within that
23 Shiga-like toxin II toxin that's so important to death and the systemic
24 complications that the subunits that make up that toxin, the alpha and then
25 there are several beta, are different in terms of their properties in terms of
26 causing disease.

27 So that we not only have the discovery that the Shiga-like toxin

1 II in human infection which is different than other animals is critically
2 important to the systemic side effects; but that the subunit A is critically
3 important to prevention of these life-threatening side effects and that it can
4 be blocked with the antibody to prevent these effects after infection has
5 occurred, after the patient is sick and that the beta subunit primarily relates
6 to the diarrhea, not the life-threatening part and, therefore, that one can
7 administer human antibody, not just to the Shiga-like toxin II specifically,
8 and keep people from developing the life-threatening complications; but that
9 if you select the alpha subunit, you can prevent the life-threatening
10 complications, not the diarrhea, not the disease in general, and that this is
11 absolutely specific to humans and that the dosage is critical and that that
12 dosage could be generally determined using this very specific baby pig
13 model where the animal does not receive Colostrum at birth.

14 So with that being said, I'm going to turn it over to Dr. Tzipori.

15 DR. TZIPORI: Thank you. I made some notes, because it's not
16 what I normally do for a living and just to make sure I keep it simple in
17 terms of the terminology as well as really the message I want to get across
18 here.

19 So I hope it won't take me too long. I have made some copies.
20 If you would like to have, I'll be happy to hand them to you.

21 The link between this bacteria 0157 and kidney failure was
22 identified in 1983. And it was shown that the infection causes bloody
23 diarrhea in people. But in a percentage of -- of infected individuals, such as
24 children in particular and the elderly, the infection can go on and, of course,
25 kidney failure.

26 And about three to six percent of those that contract and
27 develop kidney failure develop what we call HUS or hemolytic uremic

1 syndrome or kidney failure or death.

2 As a veterinarian I noticed the similarity back in 1985 between
3 this infection and an infection which occurs naturally in piglets. And in
4 collaboration with the CDC we started this work to see whether we could
5 use the pig to identify some of the characteristics that are responsible for
6 inducing the disease in one hand and the -- and the kidney damage on the
7 other.

8 And so using the pig model we were able to establish as one of
9 the two toxins that the bacteria produces which is the Stx2 -- is more critical
10 for the development of the kidney failure and that antibodies against the
11 toxin II will prevent that.

12 So we went ahead and used -- we got funded from NIH to
13 develop human antibodies in transgenic mice. Transgenic mice are special
14 mice that have been manipulated genetically to produce human antibodies
15 instead of mouse antibodies. And, hence, they are much more acceptable for
16 clinical use.

17 And -- and as a consequence of this work in 1996 we filed a
18 patent with regard to the use of this approach to treat children that are
19 presenting with bloody diarrhea; treat them with these antibodies and
20 prevent the consequence -- the consequential development of -- of HUS
21 which is the kidney failure.

22 Because of the period between the onset of diarrhea and the
23 onset of the kidney damage is about four days we felt that if these antibodies
24 are given at the onset of diarrhea or thereafter, we could protect those
25 children from developing kidney failure.

26 And this was -- that proved to be really the case, because the
27 piglet develops diarrhea first and then two days later develops neurological

1 symptoms which kind of -- really they are the same type of generic disease.
2 I don't really want to go into the physiology of it.

3 So we were able to, in fact, with the antibodies, the human
4 antibodies that we produced -- to treat piglets well after the onset of the
5 diarrhea, 48 hours, in fact, after infection, and still protect them against the
6 fatal complication that are associated with the toxin.

7 Now, the antibodies are produced against the toxin. And they
8 are given systemically -- that means by injection -- to utilize the toxin that
9 have got -- that was absorbed or got absorbed from the GI tract, from the
10 gastrointestinal tract. I just want to illustrate to you.

11 So we got as far as really -- with funding from the National
12 Institutes of Health to show that these antibodies are protective, but NIH
13 does not fund product development beyond this point as they expect the
14 private sector to license such potential therapeutic products.

15 The lack of IP for this product has so far precluded such an
16 option. This situation has changed dramatically with the emergence of
17 threats of bioterrorism after September 11.

18 The CDC and NIH have classified HUS, this disease that I'm
19 talking about, as a potential threat and funded our group to continue to
20 develop this therapeutic approach under the umbrella of countermeasure
21 development against biothreat.

22 The additional fund allowed us to really, A, generate under
23 GMP enough material to test in -- in human volunteers and also to conduct
24 the phase one clinical trials in human adult volunteer which is expected to
25 begin in two or three days -- two or three months.

26 We have institutional protocols developed by Tufts University
27 and the National Institutes of Health for adults -- for these studies in adults.

1 And it's currently pending FDA approval.

2 To illustrate the significance of the disease and the urgent need
3 for therapy I refer your attention to three outbreaks due to this infection
4 which occurred late last year. One in particular which became known as the
5 spinach outbreak originated in California's Green Growers' farm.

6 During August, September 2006 the outbreak of E. coli
7 involving 26 states occurred which affected 200 people. Half of them, 51
8 percent, were hospitalized. 31, 16 percent, developed kidney failure. 22 of
9 them were children and under five years of age. 30 percent of children
10 developed kidney failure, eight in adults and so on. Four of them died, two
11 of -- two of whom are children.

12 During this outbreak I got numerous calls from clinicians and
13 physicians inquiring about the status of our antibodies be it through -- of
14 course, through the literature.

15 And a consultant from the California legislature contacted me
16 requesting information on progress and had asked whether the California
17 legislature can be -- in any way help -- can in any way help accelerate the
18 process, to speed up the approval process and the production of this
19 treatment.

20 The truth of the matter is given the perceived limited market for
21 such a drug -- it's really classified as often a drug -- no commercial entity is
22 willing to license this product without the secured IP.

23 I could go on and touch on how we address the issue of --
24 regarding prior arts, but maybe I should leave that -- if you have any
25 questions.

26 I also have a summary of what we were able to reveal through
27 our work with regard to this infection and how the treatment fits in, but I

1 could leave that. I don't want to kind of continue with this monologue.

2 JUDGE ADAMS: Thank you.

3 MS. PABST: Okay. Then let me make a few remarks. And I
4 think we probably laid out most of our position with respect to why we think
5 this is patentable over the prior art.

6 The fact is obviously the claims are drawn to different subject
7 matter. The limitations in the claims that we think are important in
8 distinguishing the prior art -- the differences in the claims that distinguish
9 over the prior art include obviously the fact that this is to humans.

10 As is mentioned in the briefs and again must be emphasized,
11 the strings of E. coli in -- are -- E. coli -- everybody knows this -- it was
12 discovered in sewers of Austin, Texas. That shows how long I've been
13 around. And it affects everybody. It's in our gut naturally.

14 But there are differences in strains as to which strains cause
15 virulent disease. And the fact is that the strains that cause this severe disease
16 in humans are ones which attach to specific receptors in the gut.

17 So when one talks about these antibodies it's important to
18 understand that it is a small, specific group of these E. coli that actually
19 cause the disease.

20 So the antibody specificity must be to the antigen, to the SL --
21 the Shiga-like toxin II antigen in the strains which cause disease in humans.
22 That is not made clear in any of the prior art. What is also not made clear --

23 JUDGE ADAMS: Krivan -- Krivan talks about the treatment
24 of humans, but --

25 MS. PABST: He has a claim in which he says humans; but
26 Krivan -- Krivan is very different, because Krivan is a general disclosure.

27 And we acknowledge, as we did in our art, that there is general

1 disclosure that says there are multiple toxins in these E. coli; that you want
2 to make antibody to the toxin to try to block the disease.

3 This goes far beyond what's in the prior art. This is based on
4 studies which are described in great detail in the application that show that it
5 is the Shiga-like toxin II that causes the life-threatening illness.

6 It is the Shiga-like toxin II which is important for prevention of
7 development of the life-threatening symptoms after infection has occurred.

8 There is no recognition in any of the prior art of the two critical
9 features related to the Shiga-like toxin II, life-threatening complications and
10 prevention after infection.

11 Krivan is associated with prevention of disease. He is working
12 primarily with -- and there's nothing wrong with Krivan. Krivan is a good
13 reference for what it teaches which is that if you give animals that are
14 deprived of Colostrum antibody before the junctions close up that you can
15 help prevent diseases that are caused by these E. coli.

16 And, again, it's perfectly valid for what it is; but it isn't a
17 teaching, because there's no data that shows the criticality of human antigen,
18 human Shiga-like toxin II.

19 And, of course, one of the things that's -- you know, looking
20 through the record you see, the -- the toxins depending on the origin are used
21 with different names.

22 So like in the birds art that was cited here, the Shiga-like toxin
23 II there is really the Shiga-like toxin I in human -- in strains that affect
24 humans.

25 So it's very important, again, to focus on human and the Shiga-
26 like toxin II in strains that cause severe disease in humans and then focus on
27 the fact that it is the subunit A. And, of course, we know we have claims to

1 B. And we have claims specific to A.

2 In these strains in causing severe disease in humans B is
3 responsible for the diarrhea. A is responsible for the life-threatening
4 complications.

5 And, as Dr. Tzipori made clear, this product is important. It
6 will save lives. This is one of those few times when I, as an attorney, am
7 privileged to work on something that will make a difference.

8 This one is important, because there was this significantly over
9 the prior art which was based on the studies that are described in this
10 application. There were subsequent studies we submitted in further proof of
11 this.

12 The fact is that this subunit, the alpha subunit, and of the Shiga-
13 like toxin II in strains causing disease in human is what will kill these
14 people. It did kill people in 2006 and in 2005. It is a small population.
15 There's no question about it.

16 JUDGE ADAMS: If I could interrupt you.

17 MS. PABST: Sure.

18 JUDGE ADAMS: You have five minutes remaining.

19 MS. PABST: That's fine. Those are the important features. I
20 want to briefly touch on dosage. Dosage is a patentable limiting feature of
21 these claims.

22 We have a number of precedential cases that focus on the fact
23 that when you define something as an effective amount -- a dosage that is an
24 effective amount that that distinguishes it over prior art not disclosing that
25 effective dosage range.

26 For example, we have the -- and I don't know how to pronounce
27 this word -- *Aktiebolag v. Andrx Pharmaceuticals*, a fed. circuit decision in

1 2003.

2 We have in re: Halleck which was the C.C.P.A. decision in
3 1970. We have Biagro Western Sales. That's a -- just a district court
4 decision.

5 We have in re: Caldwell, C.C.P.A, 1963, Geneva Pharms --
6 Pharms, Inc., v. Glaxo Smith Kline, fed. circuit, 2003, and Minnesota
7 Mining and Manufacturing Company, the fed. circuit decision in 2002.

8 Every one of these decisions was reported -- is a decision in
9 which the language that it was an effective dosage imparted novelty and
10 nonobviousness to those claims over the prior art. It is not a meaningless
11 limitation.

12 It was not routine to discover -- the examiner has focused on
13 the fact that it would be routine to optimize the dosage, but you have to have
14 a starting point. You have to have a point at which you have efficacy in
15 treatment.

16 And that starting point is described in these examples. It cannot
17 be determined in vitro. It cannot be determined with mice. It had to be
18 determined from these pig studies.

19 And that is what the inventors did in this case. They defined
20 those starting dosage ranges. It turns out those dosage ranges are correct.
21 Those are the ones that are going to be in the clinical trials. They are
22 meaningful. And they are nowhere in the prior art. So we think that's an
23 important limitation. Do you have any questions?

24 JUDGE ADAMS: So your position would be the dosages that -
25 - I call it the Krivan --

26 MS. PABST: I'm sorry. I can't hear you.

27 JUDGE ADAMS: The K reference. Your position would be --

1 MS. PABST: I'm sorry. I still couldn't hear you.

2 JUDGE ADAMS: Your position would be that the dosages set
3 forth in the primary reference, the K reference, the Krivan reference, are not
4 -- are not equivalent to this effective amount in your claim --

5 MS. PABST: The prior art dosages cover a large dosage range
6 which would, in fact, be toxic as well as ineffective.

7 And I think it's -- I don't have -- you all know the prior -- you
8 know the case law quite well; that when you have a very large range, which
9 -- much of which is not enabled for our indication, that that does not teach
10 the selection of an effective dose range as defined by the claim.

11 And that's what these court decisions say as well; that where
12 that limitation is important, as it is in this case, and where you cannot get
13 there from the prior art that it is both novel and nonobvious.

14 And I think one other quick point which Dr. Tzipori touched on
15 is when you look at nonobviousness -- and, of course, we're all looking at
16 KSR v. Teleflex -- the fact is that this has been a disease that's been around
17 for decades, a life-threatening disease with mortalities every year.

18 There is no effective treatment. This is the only treatment that
19 the FDA is considering for treatment of this disease. There is longstanding
20 but unmet need. This product is the only one that both recognition in the
21 literature and in the scientific community --

22 JUDGE ADAMS: I missed that -- I missed that argument in
23 your brief. It's not in there, is it?

24 MS. PABST: It actually is in the brief; page 9, last paragraph.
25 Technology is very important. A need which has been known for many
26 years but which there is no accepted product available to clinicians. It's
27 being -- currently being developed using nonprofit research funds due to the

1 critical need for such a product.

2 That is the NIH funding that is being used for this. There was a
3 licensee. And when we went on appeal they terminated the relationship.
4 Because of that longstanding and unmet need the NIH stepped up on this and
5 is funding the clinical development.

6 JUDGE ADAMS: Any questions? Okay. Thank you very
7 much.

8 MS. PABST: Thank you.

9 (Whereupon, the proceedings at 9:25 a.m. were concluded.)

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